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Cannabis Sativa L as Natural Source of Promising Anti-Alzheimer Drug Candidates: A Comprehensive Computational Approach Including Molecular Docking, Molecular Dynamics, Admet and MM-PBSA Studies

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Abstract : Cholinesterase enzymes are biological catalysts essential for the transformation of acetylcholine, which is a neurotransmitter implicated in memory and learning, into acetic acid and choline, altering the neurotransmission process in Alzheimer's disease patients. Therefore, inhibition of cholinesterase enzymes is a relevant strategy for the symptomatic treatment of Alzheimer's disease. The current investigation aims to explore potential Cholinesterase (ChE) inhibitors through a comprehensive computational approach. Forty-nine phytoconstituents extracted from Cannabis sativa L were in-silico screened using molecular docking, pharmacokinetic and toxicological analysis to evaluate their possible inhibitory effect towards the cholinesterase enzymes. Two phytoconstituents belonging to cannabinoid derivatives were revealed to be promising candidates for Alzheimer therapy by acting as cholinesterase inhibitors. They have exhibited high binding affinities towards the cholinesterase enzymes and showed their ability to interact with key residues involved in cholinesterase enzymatic activity. In addition, they presented good ADMET profiles allowing them to be promising oral drug candidates. Furthermore, molecular dynamics (MD) simulations were executed to explore their interactions stability under mimetic biological conditions and thus support our findings. To corroborate the docking results, the binding free energy corresponding to the more stable ligand-ChE complexes was re-estimated by applying the MM-PBSA method. MD and MM-PBSA studies affirmed that the ligand-ChE recognition is spontaneous reaction leading to stable complexes. The conducted investigations have led to great findings that would strongly guide the pharmaceutical industries towards the rational development of potent anti-Alzheimer agents.

Keywords : alzheimer's disease, molecular docking, cannabis sativa l, cholinesterase inhibitors
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